CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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The chemicals listed in the following tables may meet the criteria for the listing of carcinogens (Table A) or reproductive toxicants (Table B) formally identified by an authoritative body, as set forth in Title 22, California Code of Regulations, Section 12306. Information on the occurrence and usage of the chemicals and the relevant references to the authoritative body publications are also given. A summary of the results of relevant studies of these chemicals follows the tables.

Table A. Chemicals Under Consideration for Possible Listing as Carcinogens

Chemical	CAS No.	Identity of chemical	Reference
Aniline hydrochloride	142-04-1	Used mainly as an intermediate in the manufacture of dyes.	US EPA (1989b)
C.I. Solvent Yellow 14	842-07-9	Monoazo dye used in a variety of substances including oils, waxes, varnishes, shoe and floor polishes, gasoline and soap.	NTP (1982a)
Carbon black (by inhalation)	1333-86-4	Widely used in rubber tires, hoses, gaskets, coated fabrics; also used in printing inks, paints and plastics.	IARC (1996)
p-Chloroaniline hydrochloride	20265-96-7	Aromatic amine widely used in the dye, chemical, textile, and rubber industries.	NTP (1989a)
p-Chloro-*o*-toluidine and its strong acid salts	95-69-2	Used in the production of azo dyes for cotton, silk, acetate and nylon and as intermediates in the production of certain pigments.	IARC (1990)
Cytembena	21739-91-3	Cytostatic agent originally tested as an anti-neoplastic drug; no current use.	NTP (1981)

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Table A (continued). Chemicals Under Consideration for Possible Listing as Carcinogens

Chemical	CAS No.	Identity of chemical	Reference
3,3′-Dichlorobenzidine dihydrochloride	612-83-9	Used mainly in the manufacture of pigments for printing ink, textiles and plastics.	NTP (1994)
Metham sodium	137-42-8	Fumigant-type pesticide used as a preplant soil fumigant, wood preservative, slimicide, tree root killer, and in weed control	US EPA (1995a)
Methyl carbamate	598-55-0	Reactive intermediate in the textile and polymer industries.	NTP (1987)
Nalidixic acid	389-08-2	Anti-microbial drug used in treatment of urinary tract infections caused by gram negative bacteria.	NTP (1989b)
o-Nitrotoluene	88-72-2	Used as a chemical intermediate and in the synthesis of dyestuffs and explosives.	NTP (1996)
o-Phenylenediamine and its salts	95-54-5	Used in the production of a variety of dyes and pigments, in the production of fungicides, and as a photographic developing agent.	US EPA (1985)
Salicylazosulfapyridine	599-79-1	Drug of choice for ulcerative colitis and Crohn's Disease; also prescribed for rheumatoid arthritis and regional enteritis.	NTP (1997)

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Table B. Chemicals Under Consideration for Possible Listing as Reproductive Toxicants

Chemical	CAS No.	Toxicological Endpoints	Identity of chemical	Reference
Acrylamide	79-06-1	developmental toxicity female reproductive toxicity male reproductive toxicity	Reactive monomer used in oil drilling, water purification, mineral processing and laboratories	NIOSH (1991, 1992) NTP (1993a)
Benzo[a]pyrene	50-32-8	developmental toxicity	Polycyclic aromatic hydrocarbon - product of incomplete combustion	IARC (1983)

Table B (continued). Chemicals Under Consideration for Possible Listing as Reproductive Toxicants

Chemical	CAS No.	Toxicological Endpoints	Identity of chemical	Reference
Boric Acid	10043-35-3	developmental toxicity female reproductive toxicity male reproductive toxicity	Pesticide, other uses in manufacturing, consumer products, and personal care products	US EPA (1993a, b)
1,3-Butadiene	106-99-0	developmental toxicity male reproductive toxicity female reproductive toxicity	Used primarily in the production of synthetic rubber.	NIOSH (1984) US EPA (1989a) NTP (1993b)
Carbon dioxide (by inhalation)	124-38-9	developmental toxicity male reproductive toxicity	Pesticide uses, food uses	US EPA (1991a, b)
o,p ' -DDT	789-02-6	developmental toxicity male reproductive toxicity female reproductive toxicity	Pesticide, environmental contaminant	IARC (1991) NIOSH (1988) US EPA (1988a)
p,p ' -DDT	50-29-3	developmental toxicity female reproductive toxicity male reproductive toxicity	Pesticide, environmental contaminant	IARC (1991) NIOSH (1988) US EPA (1988a)
DDT, technical grade	---	developmental toxicity female reproductive toxicity male reproductive toxicity	Pesticide, environmental contaminant	IARC (1991) NIOSH (1988) US EPA (1988a)
(2,4-dichlorophenoxy) acetic acid	94-75-7	developmental toxicity	herbicide (2,4-D)	US EPA (1988c)
2,4-D n-butyl ester	94-80-4	developmental toxicity	ester of 2,4-D	US EPA (1988c)
2,4-D isopropyl ester	94-11-1	developmental toxicity	ester of 2,4-D	US EPA (1988c)
2,4-D isooctyl ester	25168-26-7	developmental toxicity	ester of 2,4-D	US EPA (1988c)
Propylene gylcol butyl ether ester (of 2,4-D)	1928-45-6	developmental toxicity	ester of 2,4-D	US EPA (1988c)
2,4-D butoxyethanol ester	1929-73-3	developmental toxicity	ester of 2,4-D	US EPA (1988c)
2,4-D dimethylamine salt	2008-39-1	developmental toxicity	salt of 2,4-D	US EPA (1988c)
2,4-D butyric acid (2,4-DB)	94-82-6	developmental toxicity male reproductive toxicity	2,4-D-type herbicide	US EPA (1988c, 1994a, b)
Endrin	72-20-8	developmental toxicity	insecticide	US EPA (1980, 1992b)
Ethylene dibromide	106-93-4	developmental toxicity male reproductive toxicity	Used as a fumigant, gasoline additive and solvent.	NIOSH (1977) US EPA (1987a, b)

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Table B (continued). Chemicals Under Consideration for Possible Listing as Reproductive Toxicants

Chemical	CAS No.	Toxicological Endpoints	Identity of chemical	Reference
Linuron	330-55-2	developmental toxicity	Pesticide	US EPA (1994a, b)
Metham Sodium	137-42-8	developmental toxicity	Pesticide	US EPA (1994a, b)
Oxadiazon	19666-30-9	developmental toxicity	Pesticide	US EPA (1994a, b)
Tetraborate and its salts (including Sodium Borate)	---	developmental toxicity female reproductive toxicity male reproductive toxicity	Pesticide uses, uses in manufacturing, consumer products, and personal care products	US EPA (1993a, b)
Vinclozolin	50471-44-8	developmental toxicity	Pesticide	US EPA (1994a, b, 1988b)
Zearalenone	17924-92-4	male reproductive toxicity female reproductive toxicity	Mycotoxin produced by numerous *Fusarium* molds.	NTP (1982b) IARC (1993)

Summarized below are the relevant carcinogenesis and reproductive toxicity studies and conclusions for chemicals under evaluation as potentially having satisfied the criteria for listing under the authoritative bodies provision of Proposition 65, as set forth in 22 CCR Section 12306. Documents published by the National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC), the US Environmental Protection Agency (US EPA), and the US National Institute of Occupational Safety and Health (NIOSH), four Proposition 65 authoritative bodies, were the primary sources for the summary. The statements in bold reflect data and conclusions that appear to satisfy the criteria for the sufficiency of evidence for carcinogenicity or reproductive toxicity in subsections (e) and (g) Section 12306. The evidence for the carcinogenicity or reproductive toxicity of the chemicals is only briefly discussed here. The full citations for the primary source documents are given in this report. The primary source documents, on file at OEHHA, provide additional details on the critical studies described below.

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CARCINOGENS

Aniline hydrochloride (CAS No. 142-04-1)

Multiple positive cancer bioassays in male rats.

The US Environmental Protection Agency found sufficient evidence of carcinogenicity in animal studies using aniline hydrochloride (US EPA, 1989b). Aniline has been identified by the US EPA (1989b) as a chemical with sufficient evidence observed of carcinogenicity in animals and on this basis it was added to the Proposition 65 list on January 1, 1990 via the authoritative bodies listing mechanism.

Aniline hydrochloride was administered in the diet to CD-F rats for two years (CIIT, 1982). An increased incidence of primary sarcomas of the spleen was observed in high-dose male rats. The National Cancer Institute (NTP, 1978) exposed male and female F344/N rats to aniline hydrochloride for 103 weeks. An increased incidence of tumors of the spleen, including hemangiosarcomas was observed in male rats (0/25, 19/50, 20/46 for control, low- and high-dose groups, respectively).

C.I. Solvent Yellow 14 (CAS No. 842-07-9)

Positive cancer bioassays in male and female rats.

The National Toxicology Program (NTP, 1982a) has concluded that there is clear evidence for the carcinogenic activity of C.I. Solvent Yellow 14 in male and female F344/N rats.

NTP (1982a) exposed F344/N rats and $B6C3F_1$ mice to C.I. Solvent Yellow 14 in feed for 103 weeks. In treated rats, a dose-dependent increase in the incidence of hepatic neoplastic nodules was observed. In males, the incidence was 5/50, 10/50, and 30/50 for control, low- and high-dose groups, respectively. In female rats, the incidence was 2/50, 3/49, and 10/48. The incidences of hepatic neoplastic nodules observed in high-dose males and in high-dose females were significantly greater than that of the respective control group and the increases occurred with a statistically significant positive trend with dose in both sexes. No treatment-related tumors were observed in $B6C3F_1$ mice of either sex.

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Carbon black (by inhalation) (CAS No. 1333-86-4)

Positive cancer bioassays in multiple studies.

The International Agency for Research on Cancer (IARC, 1996) has identified carbon black as a Group 2B carcinogen based on sufficient evidence in experimental animals. IARC previously considered carbon black in 1984 and in 1987. Newly available data were taken into consideration in the current evaluation. The relevant studies are briefly described below.

Mauderly *et al.* (1994) [Nikula *et al.* (1995)] exposed male and female Fischer 344/N rats to furnace black via inhalation for up to 24 months. A statistically significant incidence of pulmonary neoplasms (adenomas and adenocarcinomas) was observed in exposed females. At low dose exposure, pulmonary neoplasms (6 adenocarcinomas and 1 adenoma) were observed in 7/107 “at risk” females (animals sacrificed prior to 12 months were not considered “at risk”). At high exposure, malignant neoplasms (primarily adenocarcinomas) were observed in 21/105 “at risk” females and combined malignant or benign tumors were observed in 28/105 females. No pulmonary tumors were observed in 105 control female rats. In male rats, no treatment-related tumors were observed.

Heinrich *et al.* (1994) exposed two groups of 72 female Wistar Crl:(WI)BR rats to furnace black by inhalation. One group was exposed for 43 weeks and maintained for an additional 86 weeks on clean air. The second group was exposed for 86 weeks and then maintained for 43 weeks on clean air. Two clean air control groups were kept for 129 weeks. No tumors were observed in the clear air control groups. In the 43-week exposure group, 13/72 rats developed lung tumors. In the 86-week exposure group, 6/72 rats developed lung tumors. Additionally, 6 rats in the 86-week exposure group showed lung lesions that were described as marked hyperplasia or marked squamous-cell hyperplasia and classified as borderline between non-neoplastic and neoplastic. IARC noted that the difference in the tumor rates in the two exposed groups was not statistically significant.

Heinrich *et al.* (1995) exposed 100 female Wistar Crl: (WI)BR rats to high purity furnace black for 24 months. After exposure, rats were kept in clean air for an additional 6 months. Control animals were exposed to clean air throughout. Mean lifespan of treated rats was significantly reduced compared to controls. There were increased benign and malignant lung tumors in the carbon black-treated group (39/100 or 28/100 if animals with only benign cystic keratinizing squamous-cell tumors are excluded) compared to controls (1/217).

Pott *et al.* (1994) exposed female Wistar rats to furnace black, administered intratracheally in 0.9% saline, once a week for 15 weeks. The animals were maintained until spontaneous death or were killed when moribund; all remaining animals were killed at 131 weeks. More than 50% of rats in the treated and control groups survived to 100 weeks. No primary lung tumors were observed in the control group. In carbon black-treated animals, 65% [24/37] of the rats had primary lung tumors.

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Heinrich (1994) exposed female Wistar rats to one of two types of extracted carbon black (furnace black or lampblack) by intratracheal injection once a week for 16-17 weeks. After an experimental period of 27 months, the respiratory tract of the 48 treated animals per group was investigated histopathologically. Of the furnace black-treated animals, 10/48 had lung tumors. Of the lampblack-treated animals, 4/48 rats had tumors described as benign cystic keratinizing squamous-cell tumors. No lung tumors were observed in vehicle-treated controls.

p-Chloroaniline hydrochloride (CAS No. 20265-96-7)

High incidence of unusual tumors in male rats.

The National Toxicology Program (NTP, 1989a) has concluded that there is clear evidence of carcinogenic activity of *p*-chloroaniline hydrochloride in F344/N male rats.

NTP administered *p*-chloroaniline hydrochloride by gavage to F344/N rats and $B6C3F_1$ mice for two years. In male rats, there were statistically significant increases in the incidences of rare sarcomas of the spleen. The incidence of fibrosarcoma was 0/49, 1/50, 2/50, and 17/50 for control, low-, mid- and high-dose groups, respectively. The incidence

of osteosarcoma was 0/49, 0/50, 1/50, and 19/50. The combined incidence of fibrosarcoma, osteosarcoma and hemangiosarcoma was 0/49, 1/50, 3/50, and 38/50. There was also a significant increase in pheochromocytomas of the adrenal gland in high-dose males compared to controls (13/49, 14/48, 15/48, and 26/49). In female rats, two rare sarcomas of the spleen were observed, but there were no significant increases in tumors. In male mice, NTP concluded that there was some evidence of carcinogenicity based on increased incidences of hepatocellular neoplasms and of hemangiosarcomas of the liver or spleen. No treatment-related tumors were observed in female mice.

p-Chloroaniline was identified by the International Agency for Research on Cancer (IARC, 1993) as a Group 2B carcinogen and was listed under Proposition 65 on October 1, 1994 via the authoritative bodies listing mechanism. The IARC designation was based on a review of both the NTP study described above and an earlier study by the National Cancer Institute (1979). In that study, rats exposed to *p*-chloroaniline in feed also developed rare fibromas and sarcomas of the spleen.

<u>*p*-Chloro-*o*-toluidine and its strong acid salts (CAS No. 95-69-2)</u>

High incidence of tumors in studies in male and female mice.

The International Agency for Research on Cancer (IARC, 1990) has identified *p*-chloro-*o*-toluidine and its strong acid salts as Group 2A carcinogens based on sufficient evidence for the carcinogenicity of *p*-chloro-*o*-toluidine hydrochloride in experimental animals and limited evidence in humans.

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p-Chloro-*o*-toluidine was listed as a Proposition 65 carcinogen on January 1, 1990 via the authoritative bodies listing mechanism. Listing was based on identification by both IARC (1983) and EPA (1986) of *p*-chloro-*o*-toluidine as an animal carcinogen in studies in which *p*-chloro-*o*-toluidine hydrochloride was tested.

The studies described below were the basis for the 1983 IARC evaluation of *p*-chloro-*o*-toluidine as a 2B carcinogen.

Weisburger *et al.* (1978) exposed CD-1 mice to *p*-chloro-*o*-toluidine hydrochloride in feed for 18 months as part of a larger study on aromatic amines; the animals were observed for an additional three months prior to sacrifice. In male mice, hemangiosarcomas or hemangiomas were observed in 12/20 low-dose and 13/20 high-dose animals compared to 0/14 in control animals and 5/99 in pooled controls from the larger study. In female mice, hemangiosarcomas or hemangiomas were observed in 18/19 low-dose and 12/16 high-dose animals (compared to 0/15 in controls and 9/102 in pooled controls).

The National Cancer Institute (NCI, 1979) exposed male and female B6C3F_1 mice to *p*-chloro-*o*-toluidine hydrochloride in feed for 92 (high-dose females) or 99 weeks. All

high-dose females died by 92 weeks. An increased incidence of hemangiosarcomas was observed in both males (0/20, 3/50, and 37/50) and females (0/18, 40/49, and 39/50).

In its 1990 evaluation, IARC included data on human carcinogenicity (bladder carcinoma in a subcohort of male employees in *p*-chloro-*o*-toluidine production and processing plants).

In formulating its overall 1990 evaluation, IARC noted "that any salt of *p*-chloro-*o*-toluidine with a strong acid can be expected to behave chemically in a manner similar to the hydrochloride salt in solution and *in vivo*" (IARC, 1990).

Cytembena (CAS No. 21739-91-3)

Positive cancer bioassays in male and female rats.

The National Toxicology Program (NTP, 1981) has concluded that cytembena is carcinogenic for male and female F344/N rats.

NTP (1981) treated F344/N rats and B6C3F_1 mice with cytembena by intraperitoneal injection three times per week for 104 weeks. Treatment-related neoplasms were observed in both male and female rats. In treated male rats, malignant mesotheliomas were significantly increased in multiple organs of the abdominal cavity compared to vehicle controls (3/50, 26/50, and 26/50 for controls, low- and high-dose animals, respectively). Mesotheliomas in the tunica vaginalis were also significantly increased (0/50, 11/50, and 10/50). NTP noted that high mortality in cytembena-treated male rats may have limited the detection of late occurring tumors.

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In female rats, a high incidence of atypical mammary gland fibroadenomas was observed. In describing these mammary lesions, NTP stated that variable degrees of cellular atypia were suggestive of early malignant transformation. It was concluded that the lesions represented a variant of mammary gland fibroadenoma. The incidence of fibroadenoma in female rats was significantly increased in the high-dose group compared to vehicle controls (13/49, 22/50, and 36/50 for vehicle controls, low- and high-dose animals, respectively).

Increased tumor incidences were not observed in B6C3F_1 mice. One mesothelioma was found in a low-dose male. It was noted that high mortality in dosed male mice may have limited the detection of late occurring tumors.

3,3′-Dichlorobenzidine dihydrochloride (CAS No. 612-83-9)

Positive cancer bioassays in multiple studies and species.

In the Seventh Annual Report on Carcinogens, the National Toxicology Program (NTP, 1994) concludes that "there is sufficient evidence for the carcinogenicity of 3,3′-dichlorobenzidine and 3,3′-dichlorobenzidine dihydrochloride in experimental animals

(IARC 1974; 1982a; 1982b)." 3,3′-Dichlorobenzidine was listed as a Proposition 65 carcinogen on October 1, 1988.

In the report NTP states that "the generic name 3,3′-dichlorobenzidine is used interchangeably with 3,3′-dichlorobenzidine dihydrochloride. Although only the dihydrochloride salt is believed to be available commercially, it was not always clear whether the salt or the free base was the compound under study" (NTP, 1994).

NTP (1994) cites the following results as evidence of the carcinogenicity of 3,3′-dichlorobenzidine and 3,3′-dichlorobenzidine dihydrochloride: "When administered in the diet, 3,3′-dichlorobenzidine induced hepatomas in male mice. When administered in the diet, the compound increased the incidences of granulocytic leukemia and Zymbal gland carcinomas in male rats and mammary adenocarcinomas in rats of both sexes. When administered in the diet, 3,3′-dichlorobenzidine induced transitional cell carcinomas of the urinary bladder in hamsters and female dogs and hepatocellular carcinomas in female dogs. When administered by transplacental exposure, the compound increased the incidences of lymphoid leukemia in mice."

Metham sodium (CAS No. 137-42-8)

Malignant tumors in male and female mice with supporting evidence in male rats.

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The US Environmental Protection Agency (US EPA, 1995a) has classified metam sodium as a B2 carcinogen based on statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse, supported by a similar tumor type (malignant hemangiosarcomas) in male Wistar rats. The relevant studies are described below.

In a study conducted by Horner (1994; cited in US EPA [1995a]), metam sodium was administered to male and female CD-1 mice in drinking water for two years. Angiosarcomas were observed in both males and females, with liver and spleen being the primary targets. In male mice, there were statistically significant increases in angiosarcomas of the liver (1/52; 8/52; 5/55; 10/52 for control, low-, mid- and high-dose animals, respectively), spleen (6/53; 3/53; 10/55; 21/53) and bone marrow [femur] (3/53; 3/53; 8/55; 15/53). The combined incidence of angiosarcomas (at all sites) in male mice was 7/52; 12/52; 12/55; 27/52. In female mice, the incidence of angiosarcoma of the spleen was significantly increased in high-dose animals compared to controls (0/55; 2/55; 4/47; 5/52). The incidence of angiosarcoma in the female liver was also increased (0/54; 0/55; 1/47; 4/52) although the increase was of borderline significance (p=0.055).

Rattray (1994; cited in US EPA [1995a]) administered metam sodium to Wistar Tox rats in drinking water for 2 years. In male rats, there was a significant increase in the incidence of hemangiosarcoma, a tumor similar to angiosarcoma, in low- and mid-dose animals (0/47; 3/49; 8/50; 3/51). No effect was seen in female rats.

Methyl carbamate (CAS No. 598-55-0)

Positive cancer bioassays in 6-, 12- and 18-month and 2-year studies in male and female rats.

The National Toxicology Program (NTP, 1987) has concluded that there is clear evidence of carcinogenic activity of methyl carbamate in male and female F344/N rats.

NTP (1987) treated F344/N rats and $B6C3F_1$ mice with methyl carbamate for 6, 12, and 18 months. A 2-year study was also conducted. In all studies, methyl carbamate was administered by gavage. In rats, neoplastic nodules of the liver were observed in all studies and hepatocellular carcinomas were observed in all but the 6-month study. In the 6-, 12- and 18-month studies, rats were treated with 0 or 400 mg/kg per day. The incidences of neoplastic nodules and hepatocellular carcinoma are shown in the table below.

Lesion	Time Period (months)	Males		Females	
		Control	400 mg/kg	Control	400 mg/kg
Neoplastic nodules	6	0/10	**6/10	0/10	*5/10
	12	0/10	**7/10	0/10	**9/10
	18	0/10	2/10	0/10	*5/10
Hepatocellular carcinoma	6	0/10	0/10	0/10	0/10
	12	0/10	**8/10	0/10	**6/10
	18	0/10	**9/10	0/10	**8/10

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*P < 0.05 compared to controls by Fisher exact test
** P < 0.01 compared to controls by Fisher exact test

In all dosed rats, hepatic cytologic alterations were observed. In the 18-month study, 9 of 10 dosed males and 2/10 dosed females died before the end of the study. Metastases were seen in 7/10 males.

In the two-year study, rats were treated with 0, 100 or 200 mg/kg per day. In female rats, treatment with methyl carbamate resulted in a statistically significant increase in the combined incidence of neoplastic nodules and hepatocellular carcinoma (0/50, 0/50, and 6/49 for control, low- and high-dose groups, respectively). In male rats, the combined incidence (4/50, 0/50, and 7/49) was not significant. The incidence in male vehicle controls (8%) was slightly higher than the NTP historical incidence in water gavage vehicle control F344/N rats (6%).

NTP's conclusions (NTP, 1987) were based on results of the 6-, 12-, 18-month and 2-year studies taken together. NTP stated that the studies "demonstrated a temporal relationship in hepatocarcinogenesis between hepatic cytologic alteration, growth of neoplastic

nodules and development of hepatocellular carcinomas. The studies showed that methyl carbamate induced histopathologic changes in a sequential manner; i.e., hepatic cytologic alteration and hyperplastic lesions appear first, followed by hepatic neoplastic nodules and then hepatocellular carcinomas."

No treatment-related tumors were observed in $B6C3F_1$ mice.

Nalidixic acid (CAS No. 389-08-2)

Positive cancer bioassays in both male and female rats with early onset in females.

The National Toxicology Program (NTP, 1989b) has concluded that there is clear evidence of carcinogenic activity of nalidixic acid in male and female F344/N rats.

NTP (1989b) administered nalidixic acid to F344/N rats in feed for two years. In male rats, statistically significant increases were observed in preputial gland neoplasms (carcinoma and adenoma). The incidence of carcinoma was 0/49, 10/49 and 12/47 for control, low- and high-doses, respectively. The incidence of adenoma was 2/49, 10/49 and 10/47 for control, low- and high-doses, respectively. In female rats, clitoral gland neoplasms (adenoma, papilloma, carcinoma or papillary carcinoma) were significantly increased compared to controls. The incidences of combined tumors were: 5/46, 15/46, and 16/47 for control, low- and high-dose groups, respectively. These neoplasms were also first detected earlier in the nalidixic acid-dosed groups (low-dose, week 73; high-dose, week 58) than in the control group (week 100). NTP reported that in both low- and high-dose females, five neoplasms were observed before week 100. In most NTP studies, clitoral gland neoplasms in untreated controls are not found before week 100. NTP noted that there were only three studies in the NTP data base in which lesions were observed before week 90 (at weeks 80, 86, and 88).

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NTP concluded that there was equivocal evidence of carcinogenic activity for male $B6C3F_1$ mice based on marginally increased incidences of subcutaneous tissue fibromas or fibrosarcomas. NTP found no evidence of carcinogenic activity in female $B6C3F_1$ mice.

o-Nitrotoluene (CAS No. 88-72-2)

Early onset of uncommon tumors in male rats.

The National Toxicology Program (NTP, 1996) has confirmed the carcinogenicity of *o*-nitrotoluene based on the development of a high incidence of mesotheliomas and a small number of cholangiocarcinomas in male rats after only 13 or 26 weeks of exposure.

In earlier studies, NTP (1992) administered *o*-nitrotoluene to F344/N rats and $B6C3F_1$ mice in feed for 13 weeks. Three of 10 male rats developed mesothelioma of the tunica vaginalis. No treatment-related tumors were observed in female rats or in mice of either sex.

NTP (1996) administered *o*-nitrotoluene to male F344/N rats in feed for 13 or 26 weeks. Of the rats exposed to *o*-nitrotoluene for 13 weeks, half were maintained on basal feed for an additional 13 weeks prior to sacrifice (stop-exposure group). In this group, 5/10 animals developed mesothelioma of the testis or epididymis compared to 0/10 in the control group. In rats exposed to *o*-nitrotoluene for 26 weeks, 7/20 animals developed mesothelioma (compared to 0/10 in the control group). In addition, 2/20 rats in the stop-exposure group developed cholangiocarcinomas. A cholangiocarcinoma was observed in a third rat in the 26-week exposure group.

NTP (1996) compared the carcinogenicity of *o*-nitrotoluene to the structurally related chemical, *o*-toluidine hydrochloride, a known animal carcinogen, which had been previously shown to cause mesotheliomas in male rats (NCI, 1979). In the current study comparing the relative potencies of the two chemicals, NTP stated that the increased incidence of mesothelioma in *o*-nitrotoluene-treated rats "indicates the relative greater carcinogenic potential or decrease in tumor latency for *o*-nitrotoluene compared to an equivalent dose and exposure time for *o*-toluidine hydrochloride" (NTP, 1996).

<u>*o*-Phenylenediamine and its salts (CAS No. 95-54-5)</u>

Positive cancer bioassays in male and female mice and in male rats.

The US Environmental Protection Agency (US EPA, 1985) has concluded that there is sufficient evidence to identify *o*-phenylenediamine (and its salts) as an animal carcinogen following oral exposure and has classified the agent as a B2 carcinogen.

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Weisberger *et al.* (1978) exposed male Charles River rats and male and female CD-1 mice to *o*-phenylenediamine dihydrochloride for 18 months via diet as part of a larger study on aromatic amines. Rats were fed a basal diet for an additional 6 months and mice for 3 months before termination of the study. *o*-Phenylenediamine exposure resulted in hepatocellular carcinomas in male rats and in mice of both sexes. In male rats, there was a significant increased incidence in the high-dose group (0/16, 0/14, and 5/16, for control, low- and high-dose animals, respectively). In pooled male controls from the larger study, the incidence of hepatocellular carcinoma was 2/111. In male mice, the incidence of hepatocellular carcinoma was significantly increased in the low-dose group (0/14, 5/17, 3/14), with the incidence in pooled controls being 7/99. In female mice, there were significant increases in hepatocellular carcinoma in both low- and high-dose groups (1/15, 6/18, 6/15). The incidence in pooled female control mice was 1/102.

US EPA (1985) also cited results from genotoxicity studies on *o*-phenylenediamine. In *Salmonella typhimurium o*-phenylenediamine was positive with metabolic activation, but not without. It was negative in a dominant-lethal assay in rats. Results from an unscheduled DNA synthesis test were positive.

Salicylazosulfapyridine (CAS No. 599-79-1)

Positive cancer bioassays in male and female mice.

The National Toxicology Program (NTP, 1997) has concluded that there is clear evidence of carcinogenic activity of salicylazosulfapyridine in male and female $B6C3F_1$ mice.

Salicylazosulfapyridine was administered to F344/N rats and $B6C3F_1$ mice by corn oil gavage for two years. NTP (1997) found some evidence of carcinogenic activity in male and female rats based on increased incidences of neoplasms in the urinary tract. In male rats, salicylazosulfapyridine treatment resulted in a significant, dose-related incidence of transitional epithelial papillomas of the urinary tract (0/50, 0/49, 2/50, 6/50, for control, low-, mid-, and high-dose groups, respectively). Papillomas were accompanied by calculi. In female rats, 2/50 mid-dose animals had urinary bladder transitional epithelial papillomas. In addition, transitional cell papillomas of the kidney were observed in 2/50 high-dose females. NTP noted that transitional epithelial papillomas of the kidney are extremely rare in female rats.

In female mice, the incidences of hepatocellular adenoma or carcinoma (combined) were significantly greater in all dosed groups than in control animals (14/50, 32/50, 28/50, 29/49). In male mice, the incidences of hepatocellular adenomas were significantly greater than in control animals (13/50, 32/50, 28/50, 42/50). In addition, the combined incidence of hepatocellular adenoma or carcinoma increased with increasing dose (24/50, 38/50, 38/50 and 44/50) in treated males.

DRAFT

REPRODUCTIVE TOXICANTS

Acrylamide (CAS No. 79-06-1)

Male reproductive toxicity **has been manifested as reduced fertility, decreased testosterone levels, dominant lethal effects, and testicular degeneration.**
Female reproductive toxicity **has been manifested as an increased frequency of fetal resorptions.**
Developmental toxicity **has been manifested as decreased birth weights and developmental neurotoxicity.**

The National Institute for Occupational Safety and Health (NIOSH, 1991) concluded that: "…acrylamide monomer may be neurotoxic, carcinogenic, genotoxic, and hazardous to reproduction. Recent studies confirm that acrylamide exposures cause cancer and reproductive effects in animals, but epidemiologic studies have not demonstrated these effects in humans." "Acrylamide exposure affected both fetal and postnatal development in mouse and rat offspring when dams were orally dosed during pregnancy. Neurotoxic effects occurred in neonates when the dam drank water containing acrylamide concentrations that were not toxic to her." NIOSH (1992) stated that: "Acrylamide is an

irritant, a potent neurotoxin that affects both the central and peripheral nervous systems, a reproductive toxin, and a carcinogen."

The National Toxicology Program (NTP, 1993a) stated that acrylamide is "known to cause reproductive toxicity, neurotoxicity, and induce dominant lethal mutations." NTP has also concluded that: "…exposure to ACRL [acrylamide] in water…resulted in slight reproductive toxicity (decreased pups/litter and spermatid head counts) and increased postimplantation loss (dominant lethal effect) in the absence of demonstrable neurotoxicity for the F_0 animals."

Adverse effects on male reproduction cited in NIOSH (1991, 1992) and NTP (1993a) consisted of testicular degeneration, decreased testosterone levels, decreased fertility, and dominant lethal effects in exposed experimental animals. Female reproductive toxicity was manifested as an increase in the fetal resorption rate in the absence of an effect on the fertility rate. Developmental effects included nerve degeneration, decreased birth weight and decreased weight gain in the offspring of animals exposed to acrylamide during pregnancy.

Benzo[a]pyrene (CAS No. 50-32-8)

Developmental toxicity **has been manifested as transplacental carcinogenicity, embryotoxicity, morphological abnormalities, and subsequent infertility of animals exposed prenatally.**

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The International Agency for Research on Cancer (IARC, 1983) concluded that: "Benzo[a]pyrene has been shown to act as a transplacental carcinogen in mice of the Ha/ICR strain (Bulay, 1970; Bulay & Wattenberg, 1971) and of the A and C57BL strains (Nikonova, 1977): lung tumors were induced in the Ha/ICR strain and liver tumours in all three strains. Transplacental carcinogenesis has also been shown in rabbits (Beniashvile, 1978).

"IARC (1983) also concluded that "Benzo[a]pyrene is embryotoxic and teratogenic in mice; the inducibility of aryl hydrocarbon hydroxylase activity in dams and fetuses is an important factor in determining these effects. A reduction in fertility in both male and female offspring was observed in mice following exposure to benzo[a]pyrene *in utero*."

Boric acid (CAS No. 10043-35-3); Tetraborate and its salts, including sodium borate

Male reproductive toxicity **has been manifested as testicular atrophy and adverse effects on sperm production.**
Female reproductive toxicity **has been manifested as decreased numbers of litters produced, and decreased numbers of corpora lutea.**
Developmental toxicity **has been manifested as reduced viability, reduced fetal weights, and an increase in the frequency of morphological variations.**

The US Environmental Protection Agency (US EPA, 1993a and 1993b) concluded that: "In chronic oncogenicity studies using mice, rats and beagle dogs, boric acid and borax were found not to be carcinogenic; however, testicular effects and decreases in body weight resulted at high dose levels." "In reproductive and developmental toxicity studies using rats, mice, and rabbits, maternal liver and kidney effects and decreased weight gain as well as decreased fetal body weights were observed. In two studies, at the highest dose levels, no litters were produced. Prenatal mortality occurred at the highest dose levels in the rabbit study." The numbers of corpora lutea were found to be decreased in a multi-generation study conducted in rats, indicating a decreased frequency of ovulation. When treated female rats were mated with control males, there was a decrease in the number of litters produced, and pup survival was compromised.

1,3-Butadiene (CAS No. 106-99-0)

DRAFT

Male and female reproductive toxicity **has been manifested as testicular and ovarian atrophy in mice following chronic exposure to 1,3-butadiene by inhalation.**
Developmental toxicity **has been manifested as morphological abnormalities in the offspring of rats exposed to 1,3-butadiene during pregnancy.**

The National Institute for Occupational Safety and Health (NIOSH, 1984) concluded: "It is recommended that 1,3-butadiene be regarded as a potential occupational carcinogen, teratogen, and as a possible reproductive hazard." "These recommendations are based on long-term animal studies which demonstrated carcinogenicity, teratogenicity and adverse effects upon the testes and ovaries."

The US Environmental Protection Agency (US EPA, 1989a) concluded that : "Chronic inhalation exposure to 1,3-butadiene…caused gonadal atrophy in both sexes of $B6C3F_1$ mice (NTP, 1984)." "Data from Hazleton Laboratories (1981b) indicate that 1,3-butadiene is a teratogen when pregnant female rats are exposed by inhalation at 8000 ppm (17,698 mg/m^3) 6 hrs/day during organogenesis."

The National Toxicology Program (NTP, 1993b) concluded: "Testicular atrophy was induced in male $B6C3F_1$ mice exposed to 1,3-butadiene concentrations of 625 ppm or above in the current studies and in previous studies." ". . . the dose-response data clearly establish the ovary as a target organ of 1,3-butadiene toxicity at concentrations as low as 6.25 ppm, the lowest concentration studied."

NIOSH (1984), US EPA (1989a) and NTP (1993b) reviewed an inhalation study performed by Hazleton Laboratories (Owen and Irvine, 1981) in which pregnant Sprague-Dawley rats were exposed to 200, 1,000, or 8,000 ppm of 1,3-butadiene for 6 hours per day on days 6-15 of gestation. Maternal body weight gain was depressed at all concentrations, and fetal growth was significantly retarded in the highest concentration group. The incidence of fetal death was increased in exposed groups, although statistical significance was not reached. Morphological abnormalities occurred at increased frequencies in exposed groups, consisting of subcutaneous hematomas, lens opacities, and skeletal anomalies. At 8,000 ppm, there was a statistically significant increase in anomalies of the skull, spine, sternum, long bones, and ribs. US EPA (1989a) also cites an abstract of a Russian study (Serebrennikov and Ogleznev, 1978) which reported that inhalation of 1,3-butadiene caused embryo mortality and teratogenesis.

Atrophy of the ovaries and testes was observed with chronic inhalation exposure to 1,3-butadiene (NTP, 1983; 1984; 1993b). Additional studies reviewed by NTP (1993b) reported sperm abnormalities in male mice exposed for 5 days (Morrissey *et al*., 1990), and gonadal toxicity in male and female mice (Melnick *et al*., 1990). NIOSH reviewed only the 1983 NTP study, and US EPA only the 1984 NTP report in assessing male and female reproductive toxicity.

Carbon dioxide (by inhalation) (CAS No. 124-38-9)

DRAFT

Male reproductive toxicity **has been manifested as impairment of sperm production.**
Developmental toxicity **has been manifested as teratogenicity and reduced viability.**

The US Environmental Protection Agency (US EPA, 1991a and 1991b) concluded: ". . . chronic studies using test animals resulted in birth defects and adverse effects on sperm production." "Deleterious effects on sperm of various animal species have been reported following exposure to high carbon dioxide atmospheres." "Serious teratological effects from acute exposure to atmospheres containing more than 10% carbon dioxide have been reported in toxicological studies.

o,*p*'-DDT (CAS No. 789-02-6); *p*,*p*'-DDT (CAS No. 50-29-3); DDT, technical grade

Male and female reproductive toxicity **has been manifested as decreased fertility, as well as adverse effects on other reproductive parameters.**
Developmental toxicity **has been manifested as decreased viability, and decreased embryonic and fetal growth.**

NIOSH (1988) concluded that: "Chronic oral administration of DDT caused decreased fertility in rats and increased mortality of their offspring . . ." "Because occupational exposure to DDT may cause adverse reproductive effects or diseases of prolonged induction-latency, the need for medical surveillance may extend well beyond termination

of employment." The document specifically identifies p,p'-DDT as the form under consideration.

US EPA (1988a) concluded that: ". . . DDT has consistently caused a decrease in the reproductive capacity in mice, rats, and dogs." Specific effects described include changes in gonads, reduced fertility, embryo and fetotoxicity, increased resorption frequency, and premature delivery. The document specifically identifies p,p'-and o,p'-DDT as the forms under consideration.

IARC (1991) concluded that: "DDT impaired reproduction and/or development in mice, rats, rabbits, dogs and avian species." Effects included reduced viability of offspring, delayed puberty, reduced fertility, changes in testicular and sperm parameters, decreased embryo size, and decreased fetal weights. Studies reviewed specifically described treatment of experimental animals with p,p'-DDT, o,p'-DDT, technical grade DDT, and the DDT-metabolite, 2,2-bis(4-chlorophenyl)ethanol-palmitic acid.

(2,4-Dichlorophenoxy) acetic acid (2,4-D; CAS No. 94-75-7); 2,4-D n-butyl ester (CAS No. 94-80-4); 2,4-D isopropyl ester (CAS No. 94-11-1); 2,4-D isooctyl ester (CAS No. 25168-26-7); Propylene glycol butyl ether ester (2,4-D PGBE) (CAS No. 1928-45-6); 2,4-D butoxyethanol ester (CAS No. 1929-73-3); 2,4-D dimethylamine salt (CAS No. 2008-39-1); 2,4-D butyric acid (2,4-DB) (CAS No. 94-82-6).

Note: For 2,4-D butyric acid (CAS No. 94-82-6) see below for discussion of additional supporting information for developmental toxicity, as well as information providing support for male reproductive toxicity.

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The *developmental toxicity* of 2,4-D and certain of its derivatives has been evidenced by embryotoxicity.

The US Environmental Protection Agency (US EPA, 1988c) concluded that, "Teratogenicity testing has been conducted with 2,4-D, several of its esters (n-butyl, isopropyl, isooctyl, PGBE, butoxyethanol), the dimethylamine salt, and 2,4-D butyric acid in mice, rats and hamsters (Courtney, 1977; Khera and McKinley, 1972; Schwetz et al., 1971; Unger et al., 1981; Konstantinova et al., 1976; Collins and Williams, 1971). Overall these studies indicate that 2,4-D and its derivatives are embryotoxic but only weakly teratogenic or nonteratogenic." All of the studies cited by the EPA document are reviewed in detail. Information such as species and number of animals used; doses, route, and days of treatment; and details of toxicological findings is provided.

2,4-DB (4- [2,4-Dichloro-phenoxy] butyric acid; CAS No. 94-82-6)

NOTE: 2,4-DB is included in the group of 2,4-D derivatives immediately above. The following information provides additional support for developmental toxicity, as well as information providing support for male reproductive toxicity.

***Developmental toxicity* has been manifested as morphological abnormalities, stillbirths, and increased post-implantation loss. *Male reproductive toxicity* has been manifested as aspermatogenesis.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "…there is sufficient evidence for listing 2,4-DB on EPCRA section 313(d)(2)(B) based on the . . . reproductive and developmental toxicity data for this chemical."

Supporting reproductive documentation for the TRI listing (US EPA, 1993d) states, "animals [dogs] exposed to 25 mg/kg/day (the LOAEL) and higher doses caused aspermatogenesis within the first 3-9 weeks of treatment (IRIS, 1993)." In addition, supporting documentation for developmental effects states, "Rats orally exposed to 17 mg/kg during gestation days 1-7 developed unspecified abnormalities; there was also an increase in stillbirths at this dose level (RTECS, 1993). In a separate study, rats orally exposed to 416 mg/kg on gestation days 5 or 9 exhibited increased pre-implantation loss and/or fetotoxicity."

DRAFT

An RfD is based on the adverse effects observed in the subchronic dog study which are summarized in IRIS (US EPA, 1992a). However, the primary toxic endpoints were internal hemorrhage and mortality, rather than aspermatogenesis. The rat data used as supporting documentation for the TRI listing are from a previously published study (Sokolova, 1976). Upon translation of the Sokolova (1976) study, it was noted that there are errors in RTECS (1997) regarding the dose and exposure duration at which developmental abnormalities and stillbirths were observed. The dose at which these adverse effects were seen occurred at 3.4 mg/kg, rather than 17 mg/kg as reported in RTECS (1997). The exposure time was translated as "throughout gestation", rather than days 1-7 as reported in RTECS (1997).

For the dog subchronic study, IRIS (US EPA, 1992a) states that "The two higher doses [25 and 80 mg/kg bw/day] produced frank effects including death, hemorrhage throughout the body, and aspermatogenesis within 3-9 weeks of treatment. Slightly increased liver-to-body weight ratios were observed at both lower dose levels, but no gross or microscopic pathology was evident."

In the rat teratology studies by Sokolova (1976), oral administration of 3.4 mg/kg/day of 2,4-DB throughout pregnancy significantly increased the number of stillborn and increased the number of young per litter while decreasing birth size. Oral administration of 1 mg/kg/day during gestation resulted in increased frequency of hemorrhages into the abdominal cavity; 0.1 mg/kg/day was considered the threshold for embryotoxic effects.

Single oral administration of 416 mg/kg at various periods of pregnancy resulted in increased frequency of pre-implantation death when given on either day 4 or 5, increased frequency of post-implantation death when given on day 9, and decreased birth size when given on either day 4, 5, 10 or 14.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:** a) dog subchronic study - US EPA (1992a [IRIS database]) gives medium confidence for the principal study b) rat teratology studies - core grade unknown, but appears to be supplemental at best.
2. **Route of administration:** a) dog subchronic study - oral, in diet, b) rat teratology study - oral gavage, in corn starch solution.
3. **The frequency and duration of exposure:** a) dog subchronic study - continuous, in diet for 90 days total, b) rat teratology study - throughout gestation for the low doses (0.1, 1, 3.4 mg/kg/day) and single administration on either day 4, 5, 7, 9, 10, 11, or 14 of gestation for the high dose (416 mg/kg).
4. **The numbers of test animals:** a) dog subchronic study - 4 per sex per group, b) rat teratology study - the number of animals per dose group was not given. However, the total number of females, males, fetuses and pups used in the studies were 283, 51, 1615, and 660, respectively.
5. **The choice of species:** The dog and rat are standard test species.
6. **The choice of dosage levels:** a) dog subchronic study - 0, 2.5, 8.0, 25, 80 mg/kg/day, b) rat teratology study - 0, 0.1, 1, 3.4 mg/kg/day throughout gestation or single administration of 416 mg/kg during gestation.
7. **Maternal toxicity:** a) dog subchronic study - not applicable, b) rat teratology study - At a dose of 3.4 mg/kg/day there was an increase in ascorbic acid levels in maternal brain tissue, but it is unclear whether this could be considered a toxic effect. Maternal toxicity was not discussed in the study following single administration of 416 mg/kg during gestation.

DRAFT

<u>Endrin (CAS No. 72-20-8)</u>

The *developmental toxicity* of Endrin has been evidenced by embryolethality, morphological malformations, growth deficits, and changes in behavior.

The US Environmental Protection Agency (US EPA, 1980) concluded that, "Because endrin has been shown to cause teratogenic effects, pregnant women, particularly those whose diets may contain large amounts of fish, must also be considered a special group at risk." In a Drinking Water Criteria Document for Endrin, US EPA (1992b) concluded, "Prenatal exposure to endrin elicited terata, mortality and/or reduced neonatal weight or weight gain in offspring of hamsters and mice. These outcomes were not consistently observed in rats. However, evidence of altered behavioral development, measured by

maze locomotor activity, was observed in offspring of rats, mice and hamsters following prenatal endrin exposure."

A number of studies conducted in experimental animals were reviewed in the 1980 US EPA document. Information such as species and strain used; route, dose, and treatment schedule; effective and no effect levels; and details of toxicological effects is provided. Of the species tested, hamsters appear to be the most sensitive. Effects observed include fetal death, growth retardation, soft tissue and skeletal malformations, and altered behavior (Chernoff, et al., 1979; Gray et al., 1979; Ottolenghi et al., 1974). Developmental toxicity has also been observed in rats and mice exposed to endrin prenatally. Fetal survival was reduced in both species (Nodu et al., 1972), and malformations have been observed in treated mice (Nodu et al., 1972; Ottolenghi et al., 1974). US EPA (1992b) also discussed the Chernoff et al. (1979) and Ottolenghi et al., (1974) studies in detail, along with a number of additional studies. Details of species, strain, and numbers of animals per dose group; route, dose, and days of treatment; and toxicological effects on offspring and maternal animals are provided in tabular form.

Ethylene dibromide (EDB) (CAS No. 106-93-4) (developmental and male reproductive toxicity

Male reproductive toxicity **has been manifested as sperm abnormalities and impaired male reproductive parameters as demonstrated in EDB-exposed rats and bulls.** ***Developmental toxicity*** **has been manifested as reduced viability and increased frequencies of skeletal abnormalities.**

DRAFT

The National Institute for Occupational Safety and Health (NIOSH, 1977) concluded: "The possible health effects of employees chronically exposed to ethylene dibromide may include the induction of cancers, malformations and heritable changes in offspring, and sterility." The NIOSH (1977) document goes on to state: "[results in male chickens are] in contrast to the effects reported in two mammalian species, cattle and rats, in which definite impairments of the male reproductive system have been noted." ". . . the anomalies in both rat and mouse fetuses from ethylene dibromide-exposed dams were significantly different from those produced by malnourishment alone when both were compared with those found in fetuses from control dams. From these data, it is evident that ethylene dibromide caused fetal abnormalities in mice and rats that were not caused by malnourishment alone."

The US EPA (1987a) concluded: "Two inhalation studies (Short *et al*., 1976; 1978) reviewed in detail by the US EPA (1984; 1985), indicate that ethylene dibromide is teratogenic in rats and mice." The Agency also concluded in a Drinking Water Criteria Document (US EPA, 1987b): "The documented antispermatogenic effect of EDB in mammals indicates that human males should be regarded as a population at special risk."

Both US EPA documents (1987a; 1987b) discuss two developmental toxicity studies by Short *et al*. (1976; 1978); NIOSH (1977) discusses only the earlier of the two papers.

Short and coworkers (1976) exposed pregnant CD rats and mice by inhalation to 32 ppm EDB for 23 hrs/day on days 6 - 15 of gestation. There were feed-restricted as well as *ad-lib* fed controls. There were no increases in maternal mortality, but treated dams of both species showed significant reductions in food consumption and body weight gain. There were no effects on fetal weight in either species. Litter size was significantly decreased in exposed rats, but not mice. A significantly increased incidence of hydrocephaly, wavy ribs and extra ribs was observed in the pups of rats exposed to EDB during gestation. These anomalies were not observed in untreated, feed-restricted rats. Similar abnormalities were observed in mice, with EDB as well as with the restricted diet. In a follow-up study (Short *et al*., 1978) the same protocol was used to expose pregnant animals to 0, 20, 38, or 80 ppm EDB. At the high concentration, maternal mortality was 50 and 100% for rats and mice, respectively. For mice exposed to 38 ppm, maternal mortality was 41%. Resorption frequency was significantly increased in mice at all concentrations, and in rats at 80 ppm. Fetal body weights were decreased in rats exposed to 38 ppm, and in mice at 20 and 38 ppm.

Reductions in semen density and sperm motility, and increased frequencies of abnormal sperm have been observed in bulls given EDB orally or by injection (Amir & Volcani, 1965; Amir, 1973; 1975). Edwards and coworkers (1970) gave EDB to male rats at a dose of 10 mg/kg by the intraperitoneal route for 5 consecutive days. Sequential matings to untreated females demonstrated that the males were completely sterile during the fourth week following treatment, but recovered thereafter. The effect was attributed to selective damage of spermatid cells by EDB. All of the studies described above were discussed by both NIOSH and US EPA. Additional studies were discussed in the two US EPA documents (1987a; 1987b) and considered to support the conclusion that EDB exposure adversely affects the male reproductive system.

DRAFT

Linuron (330-55-2)

Developmental toxicity **has been manifested as decreased fetal body weights and viability, and an increase in skull malformations.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing linuron on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available hematological and developmental toxicity data for this chemical." Supporting documentation for this listing (US EPA, 1993c) states, "In a separate teratogenicity feeding study in rats, a LOAEL of 31.25 mg/kg/day was based on an increased incidence of resorptions; the LOAEL for maternal toxicity in this study was 6.25 mg/kg/day (NOEL 2.50 mg/kg/day) based on decreased food consumption and decreased body weight gain. An oral teratology study in rabbits indicated a LOAEL of 5 mg/kg/day (lowest dose tested) based on decreased fetal body weight, decreased litter size and an increase in skull malformations (IRIS, 1993)."

The *Reregistration Eligibility Decision* document (RED; US EPA, 1995b) discusses the same two developmental toxicity studies. In both IRIS and the RED document, the same

adverse effects on development are reported. However, for both studies, there are differences between the two US EPA documents in the doses reported as effective.

> For the rat study, the RED document states, "The NOELs for maternal systemic toxicity and developmental toxicity were 125 ppm (12.1 mg/kg/day). The LOEL of 625 ppm (49.8 mg/kg/day) for maternal systemic toxic effects was based upon decreased body weight and food consumption values. The developmental toxicity LOEL of 625 ppm (49.8 mg/kg/day) was based on increased in postimplantation loss and increases in the litter and fetal incidences of resorptions."
>
> For the rabbit study, the RED document states, ". . . a maternal systemic toxicity LOEL was observed at the 25 mg/kg/day level, based upon reduced maternal body weight, thereby defining the NOEL as 5 mg/kg/day. At the high-dose level (100 mg/kg/day) maternal body weight, food consumption, absolute liver weight, and liver-to-body weight ratios were decreased. The developmental toxicity NOEL was determined to be 25 mg/kg/day, based upon an increased number of abortions, decreased mean number of fetuses per litter, decreased fetal body weight, and increased incidence of fetuses with skeletal variations of the skull at the 100 mg/kg/day level (the developmental toxicity LOEL)."

Based on the results of these studies, US EPA (1995) concluded, "Due to the short-term and intermediate-term endpoints based on maternal and developmental concerns, the Agency is requiring minimum handler personal protective equipment requirements for any end-use product containing linuron."

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With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA Toxic Release Inventory list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:** a) rat developmental toxicity study - the US EPA (1995) *RED* document states that this study satisfies guideline requirements. b) rabbit developmental toxicity study - the US EPA (1995) *RED* document states that this study satisfies guideline requirements.
2. **Route of Administration -** Oral
3. **The frequency and duration of exposure:** a) rat developmental toxicity study - each of gestation days 6 -15. b) rabbit developmental toxicity study - each of gestation days 7 through 19.
4. **The numbers of test animals:** Not stated for either study. However, guidelines require a minimum of 20 rats or 12 rabbits per dose group.
5. **The choice of species:** The rat and rabbit are standard test species.
6. **The choice of dosage levels:** a) rat developmental toxicity study - 0, 5.0, 12.1, 49.8 mg/kg/day, b) rabbit developmental toxicity study - 0, 5, 25, 100 mg/kg/day
7. **Maternal toxicity:** In both studies, it cannot be concluded that developmental toxicity is secondary to maternal toxicity. In the rabbit study, the evidence for

maternal toxicity was primarily reduced maternal body weights. It should be noted that gestational weight gain in rabbits is known to be highly variable, and is therefore not generally considered an accurate indication of maternal toxicity. More generally, US EPA *Guidelines for Developmental Toxicity Risk Assessment* (US EPA, 1991c) state, "Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity; rather when the LOAEL is the same for adult and developing organisms, it may simply indicate that both are sensitive to that dose level."

Metham Sodium (000137-42-8)

Developmental toxicity **has been manifested as postimplantation loss in rabbits, and as increased variations, retardations, and anomalies in rats.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing metham sodium on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data for this chemical and its metabolite, carbon disulfide." Supporting documentation for this listing (US EPA, 1993c) states, "The Peer Review Committee concluded that metam sodium induces developmental toxicity in two species (rat and rabbit) although neither study was considered to be fully adequate due to study design and reporting deficiencies." "In addition, metam sodium is metabolized to carbon disulfide, a potent developmental toxicant."

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The species, doses, routes and periods of exposure, and effects observed in the studies described in the supporting documentation are consistent with two studies accepted for registration purposes by the California Department of Food and Agriculture (CDFA, 1986), and reviewed by OEHHA staff in relation to the spill of metam sodium into the upper Sacramento River. Two additional studies which were reviewed by OEHHA staff in this context (OEHHA, 1992), did not alter the weight-of-evidence determination concerning the developmental toxicity of metam sodium.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:** US EPA's Peer Review Committee concluded that there were deficiencies of study design and reporting, but that the weight of evidence still supported a finding that Metham Sodium adversely affects development. CDFA (1986) judged the studies to be acceptable for registration purposes in California, after additional information was submitted. No major deficiencies in study design were noted by staff in the Reproductive Toxicology Unit of RCHAS during preparation of the OEHHA (1992) review.
2. **Route of administration:** Oral

3. **The frequency and duration of exposure:** Rabbits were treated on each of gestation days 6 - 18, rats on days 6 - 15, consistent with what has been the required standard for such regulatory studies.
4. **The numbers of test animals:** Cannot be determined from the information available in the US EPA supporting documentation, but is reported in the original studies and the CDFA summary to be 15 rabbits/group and 25 rats/group. These numbers meet or exceed the minimum number of animals per group which has been required for such regulatory studies.
5. **The choice of species:** Rats and rabbits are standard test species for developmental toxicology.
6. **The choice of dosage levels:** Rabbits: 0, 10, 30 or 100 mg/kg/d. Rats: 0, 10, 40 or 120 mg/kg/d. The developmental LOEL in rabbits was 30 mg/kg/day, with a NOEL of 10 mg/kg/day. The developmental LOEL in rats was 10 mg/kg/day, with no NOEL identified. The choice of dose levels was such that a hazard could be identified.
7. **Maternal toxicity:** Maternal toxicity is not mentioned in the US EPA supporting documentation. DPR identified maternal NOELs of 30 and 10 mg/kg/day for rabbits and rats, respectively, which are higher than the corresponding developmental NOELs identified in these studies (i.e., developmental toxicity was observed at exposure levels that resulted in no observed maternal toxicity). OEHHA (1992) concurred with these values in its review.

DRAFT

Oxadiazon (CAS No. 019666-30-9)

Developmental toxicity **has been manifested as increased fetal resorptions in rats.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing oxydiazon [sic] on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental, hepatic, and renal toxicity data for this chemical." Supporting documentation for this listing (US EPA, 1993c) states, "Rats given 40 mg/kg/day by gavage on days 6 to 15 of gestation exhibited increased fetal resorptions. The NOEL was 12 mg/kg/day."

The CDFA (1987) "Summary of Toxicology Data for Oxadiazon" describes a rat developmental toxicity study which appears to be the same as that discussed by US EPA (same effect at the same dose). It is categorized as acceptable. Two rabbit studies are also summarized by DPR, one was considered to be unacceptable, the other was considered acceptable and to demonstrate adverse effects on development.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:** The rat developmental toxicity study used doses of 0, 3, 12, or 40 mg/kg/day by gavage to groups of 20 mated Sprague-Dawley rats, on gestation days 6 - 15. Generally, this design appears to meet the specifications of FIFRA test guidelines (US EPA, 1983). The rat study was determined to be acceptable by CDFA.
2. **Route of Administration** - Oral
3. **The frequency and duration of exposure:** Stated to have been daily on gestation days 6 - 15, consistent with what has been the required standard for regulatory studies of this type conducted in the rat.
4. **The numbers of test animals:** Stated to have been 20 animals per group, which corresponds to requirements of the current draft Health Effects Test Guidelines (US EPA, 1995c).
5. **The choice of species:** The rat is a standard test species.
6. **The choice of dosage levels:** The LOEL for effects was 40 mg/kg/day, the NOEL was 12 mg/kg/day. The choice of dose levels was such that a hazard could be identified.
7. **Maternal toxicity:** It is specifically stated that no maternal toxicity was observed.

Tetraborate and its salts, including sodium borate

A discussion on tetraborate and its salts, including sodium borate is provided within the previous discussion on boric acid.

DRAFT

Vinclozolin (CAS No. 050471-44-8)

Developmental toxicity **has been manifested in treated rats as pseudohermaphroditism of male offspring, developmental delays, reduced male and female pup weight, and increased stillbirths.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: ". . . there is sufficient evidence for listing vinclozolin on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available endocrine, adrenal, renal, hepatic, and developmental toxicity data." Supporting documentation for this listing (US EPA, 1993c) states, "Pseudohermaphroditism (a decrease in anal-genital distance) occurred in male offspring of rats administered doses of 50 mg/kg (the LOEL) and higher by gavage. The developmental NOEL was 15 mg/kg ([ref.] 24). The same effect was noted in the offspring of rats that received dermal applications of 180 mg/kg/day (LOEL). The developmental NOEL was 60 mg/kg/day during gestation, and also in a 2-generation reproduction study in rats (LOEL 86 mg/kg/day, NOEL 25 mg/kg/day) (24 [this refers to the Tox One-liner database, cited below]). Other developmental effects observed in the latter study included developmental delays, reduced male and female pup weight, increased stillbirths and increased pup mortality throughout lactation."

The supporting document cites the US EPA Office of Pesticide Programs (OPP) " Tox-One-Liner Database (sanitized version), 1993". A copy of the US EPA's tox one-liner for this compound, dated 6/20/94 (1994c) , describes several reproductive and developmental toxicity studies, including those cited in the TRI proposed and final rules.

An additional US EPA document, the Proposed Rule for Pesticide Tolerances for 3-(3,5-Dichlorophenyl)-5-Ethenyl-5-Methyl-2,4-Oxazolidinedione (Vinclozolin) (53 FR 41209, 1988b), lists two developmental toxicity studies which also demonstrated adverse effects. A mouse study was said to have a NOEL for maternal toxicity of 900 mg/kg/day, and a NOEL for developmental toxicity of 90 mg/kg/day. A rabbit study was said to have a NOEL for maternal toxicity of >300 mg/kg/day, and a NOEL for developmental toxicity of 80 mg/kg/day. No further detail was provided on these studies.

With regards to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:** US EPA considered these studies to be suitable for risk assessment purposes. RCHAS has no information in contradiction to US EPA's conclusions.
2. **The route of administration:** oral and dermal
3. **The frequency and duration of exposure:** a) Oral developmental toxicity study, rat: not stated. FIFRA test guidelines require a minimum exposure period of treatment on each of gestation days 6 - 15 (US EPA, 1983a). b) Dermal developmental toxicity study, rat: not stated. Specific FIFRA test guidelines for dermal developmental toxicity studies were not in place at the time of evaluation. c) Oral reproductive toxicity study, rat: While the frequency and duration of exposure are not specifically stated, it is stated that this was a multigeneration feeding study. The normal practice in studies of this type is to make treated feed the only available food source to the animals for the duration of the study. It should be noted that the minimum frequency and duration of exposure are of importance in evaluating the quality of studies where *no* effect is identified. When effects are identified, they may have been the result of a single exposure - on any of the specific treatment days. Particularly in the case of an unusual and serious defect, such as pseudohermaphrodatism, the findings would in no way be invalidated even if treatment were only given on a single day.
4. **The numbers of test animals:** a) Oral developmental toxicity study, rat: not stated. FIFRA test guidelines require a minimum of 20 rats per group (US EPA, 1983a). b) Dermal developmental toxicity study, rat: stated to be 25 rats per dose group. c) Oral reproductive toxicity study, rat: not stated. FIFRA test guidelines require a minimum of 20 animals per dose group (US EPA, 1983b).
5. **The choice of species:** Rats are a standard test species.
6. **The choice of dosage levels:** a) Oral developmental toxicity study, rat: doses tested by gavage are stated to have been 0, 15, 50, 100, 150, and 200

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mg/kg/day. b) Dermal developmental toxicity study: doses tested are stated to have been 0, 60, 180, and 360 mg/kg/day. c) Oral reproductive toxicity study, rat: Concentration levels in feed were 0, 50, 300, 1000, and 3,000 ppm.

7. **Maternal toxicity:** Maternal toxicity is not mentioned. However, it seems worth noting that if pseudohermaphrodatism could be caused by generalized maternal toxicity, it should be observed in any study where maternal toxicity occurs. In fact, it is not.

Zearalenone (CAS No. 17924-92-4) (male and female reproductive toxicity)

Male and female reproductive toxicity **has been manifested as abnormalities of male and female reproductive organs, such as testicular atrophy, inflammation of the prostate, uterine fibrosis and mammary cystic ducts.**

The National Toxicology Program (NTP, 1982b) concluded that: "Administration of zearalenone was related to the occurrence of inflammation of the prostate, testicular atrophy, and cytoplasmic vacuolization of the liver in F344/N rats and to nephrosis in rats of either sex. In female $B6C3F_1$ mice, zearalenone increased the incidence of bone marrow myelofibrosis, uterine fibrosis, and mammary cystic ducts." NTP (1982b) noted that zearalenone and zearalenol have been shown to bind to the uterine cytoplasmic estrogen receptors of Holtzman and Sprague-Dawley rats and to elicit the translocation of the cytosol-receptor complex to the nucleus (Katzenellenbogen *et al*., 1979; Kiang *et al*., 1978). Zearalenone has also been found to bind to the mammary gland estrogen receptors of Sprague-Dawley rats (Boyd and Wittliff, 1978). NTP (1982b) went on to conclude that: "The physiological consequences of these subcellular events were shown clearly in the subchronic tests." "Effects on the pituitary, prostate, testes, and bone in rats may also be linked to the binding of zearalenone or its metabolite to steroid receptors."

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The International Agency for Research on Cancer (IARC, 1993) concluded: "Zearalenone has oestrogenic effects in domestic pigs and experimental animals." "Zearalenone given in the diet of mice for 13 weeks caused atrophy of seminal vesicles and testes, squamous metaplasia of the prostate gland, osteoporosis, myelofibrosis of the bone marrow, cytoplasmic vacuolization of the adrenal glands, hyperkeratosis of the vagina and endometrial hyperplasia. Rats are about 10 times more sensitive than mice, (NTP, 1982b). Swine are the most sensitive domestic animals; for example, dietary levels of zearalenone as low as 5 mg/kg induce pseudopregnancy with a failure to cycle (Eteinne and Jemmali, 1982)." "The visible signs of zearalenone-induced hyperoestrogenism in female swine are swollen vulva and mamma, enlargement of the uterus, ovarian changes and infertility (Mirocha and Christensen, 1974; Bauer *et al*., 1987). The no-observed-adverse-effect level is less than 5 mg/kg bw (Farnworth and Trenholm, 1983)."

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